Annals of the Rheumatic Diseases, 1986; **45**, 417–421

Wegener's granulomatosis in two sisters

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SUMMARY We describe two sisters with necrotising granulomas. The intervals between the onset of symptoms and diagnosis were eight and nine years. The pathological findings showed necrotising granulomas in both patients, this being consistent with a diagnosis of pathergic (Wegener's) granulomatosis. The one patient that accepted treatment responded well to cyclophosphamide, though the facial lesions responded only to radiation therapy. Since the second was almost asymptomatic we conclude that relatives of patients with Wegener's disease should be investigated.

Key words: cyclophosphamide, radiation therapy, necrotising granuloma, pathergic granulomatosis.

Wegener's disease, although rare, has over the past few years been the subject of a number of reviews. Even though our knowledge of its aetiology and pathogenesis has increased only slightly, the finding that cyclophosphamide can induce a complete remission of the disease has encouraged its study. Besides the classical form of Wegener's disease, characterised by its rapid and fatal course without therapy, other forms have also been recognised.

Fienberg, in 1955,[1] and Carrington and Liebow, in 1966,[2] described a localised form of this disease. At first, this type of Wegener's disease was thought to involve only the lungs, and even today some consider this to be the case.[3] Nevertheless, the more extensive reviews indicate that the disease can affect other organs as well as the lungs.[4] There remains a lack of uniformity in the nomenclature of these forms of the disease as localised, pathergic, or indolent Wegener's.[5] Possibly all these names refer to the same disease.

There are differences between generalised and pathergic Wegener's disease. The latter form is localised to one or two organs, and many patients are diagnosed only months or years after the onset of the disease. Besides this, vasculitis is almost always present in the generalised form, but typical pathergic Wegener's disease may occur without vasculitis.[6] In spite of these differences both pathergic and classic forms of Wegener's are considered to be the same disease.

We have not found reports of any familial association of this disease, which may be due to the small numbers described. Nevertheless, it is interesting that Elkon *et al* have found an increase in the incidence of HLA-DR2 in the generalised form of Wegener's disease, though not in polyarteritis nodosa or in Churg-Strauss syndrome.[7]

We describe here two sisters with Wegener's granulomatosis whose disease started early in life.

Case reports

CASE 1

A 20 year old woman, born by normal delivery, had measles and chickenpox as a child. Her health was good up to the age of 8, when she developed fever, epistaxis, and nasal congestion. A polypectomy was performed without much relief, and the symptoms, which include frequent episodes of otitis media, have persisted up to the present.

At the age of 12 the patient noted three small nodules on her cheek. One of these ulcerated and scarred spontaneously after a few weeks of topical therapy. At the age of 14 saddle nose deformity developed, with a slow but progressive destruction of the nasal septum. Many biopsies of the nose were performed, and histology showed a granulomatous reaction. All cultures were negative, but treatment with tuberculostatic drugs was given for nine months without any response. In October 1979 (at the age of

Accepted for publication 10 October 1985.
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15) a nodule appeared on the right buttock. It ulcerated and did not disappear either with topical treatment or with systemic corticosteroids.

In February 1981 the patient was seen for the first time in the Department of Internal Medicine of this hospital. At that stage she had a persistent cough, thick septum, fever, and dyspnoea. Physical examination showed marked shrinkage of the nose, with small ulcers on the borders of the nostrils. There were two small nodules (1×1 cm) on the cheeks and a small scar of the nodule that had formed a fistula at the age of 12.

On the right buttock she had a large ulcer (5×10 cm) and also some small nodules on the hands and feet. All these subcutaneous nodules were firm and non-painful, and the overlying skin was dark purple in colour. The heart was normal. Some rales were heard at the left pulmonary base. The abdomen was unremarkable. She did not have alopecia, Raynaud's phenomenon, or arthritis.

Ear, nose, and throat examination showed perforation of the nasal septum and of the right tympanic membrane. Sinus *x* rays showed opacification of the maxillary and frontal sinuses and the mastoid area. On chest *x* ray a small alveolar infiltrate was seen on the left pulmonary base, with a partial collapse of the left inferior lobe (Fig. 1).

Laboratory results showed: erythrocyte sedimentation rate (ESR) 30 mm/1st h; Hb 13·6 g/dl (136 g/l); total leucocytes $8{\cdot}7\times10^9$/l, with 40% lymphocytes, 55% neuthrophils, and 5% monocytes; creatinine 46 µmol/l; glucose 5 mmol/l; uric acid 0·15 mmol/l; serum aspartate transaminase 40 U/l; alkaline phosphatase 70 U/l. The protein electrophoretic pattern showed that IgA, IgG, and IgM were normal. Tests for antinuclear antibodies, rheumatoid factor, and anti-DNA antibodies were all negative; serum C3 and C4 levels were normal. Urine analysis showed a specific gravity of 1·020, with no trace of albumin and a normal sediment.

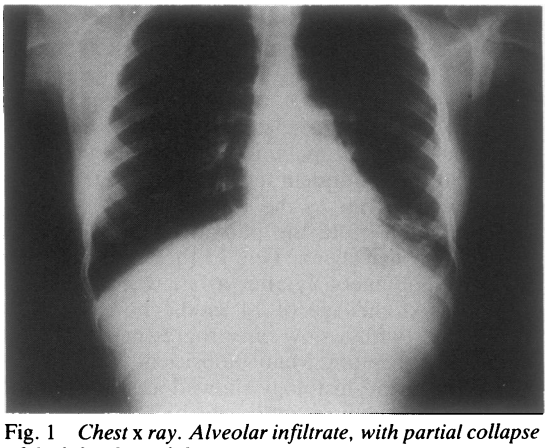

Fig. 1 *Chest x ray. Alveolar infiltrate, with partial collapse of the left inferior lobe.*

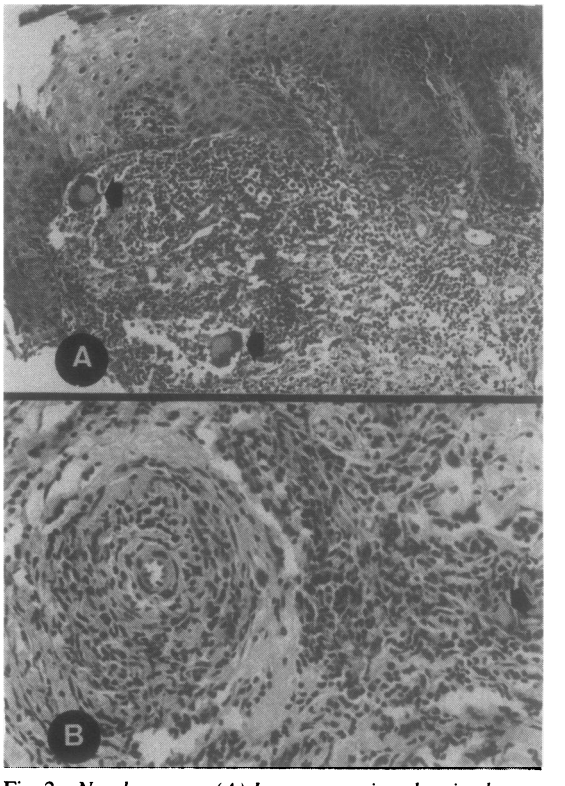

Fig. 2 *Nasal mucosa: (A) Low power view showing heavy inflammatory mononuclear cell infiltration with giant cells (arrows). (H & E, ×70). (B) The infiltrate is composed of lymphocytes, monocytes, and occasional giant cells (arrow). There are also small blood vessels surrounded by lymphocytes. (H & E, ×70).*

Repeated biopsy specimens of the ulcer, normal skin, and nasal mucosa were obtained. The first mucosal biopsy specimen showed loose mucoid stroma, with abundant lymphocytes, plasma cells, and eosinophils covered by respiratory epithelium with thickened basement membrane, all the features being consistent with an allergic polyp. The second nasal biopsy specimen from the septum showed intense lymphocytic and monocytic infiltration, with occasional giant cells and prominent lymphocytic infiltration around small and medium sized blood vessels (Fig. 2). The skin biopsy specimens showed ulceration necrosis, intense lymphocytic and monocytic infiltration, with occasional giant cells and perivascular lymphocytes.

An extensive search in the biopsy specimens and secretion samples showed no signs of fungus, parasites, brucella, or mycobacteria. The patient refused a lung biopsy, and in March 1981 treatment with 4 mg/kg cyclophosphamide was started. After 15 days of treatment the ulcer on the buttock (which had been open for the previous 16 months) healed, the fever disappeared, and the subcutaneous nodules had diminished in size. Initially, there was a slight improvement in the nasal congestion and dyspnoea. After eight months of therapy, however, the facial lesions became progressively worse, and there was no definite improvement in the respiratory symptoms. The dose of cyclophosphamide used (generally 3 mg/kg) was that necessary to maintain the leucocytes in a range of $2{\cdot}5-3{\cdot}0\times10^9$/l.

In October 1981 pulmonary function tests showed a significant ventilatory insufficiency with considerable restrictive component and an increase in elasticity. A lung biopsy was performed and this showed several necrotic foci, with intense lymphocytic, monocytic, and neutrophil infiltration (Fig. 3). No mycobacteria or fungus were found. Prednisolone 60 mg/day was added to the current cyclophosphamide dose.

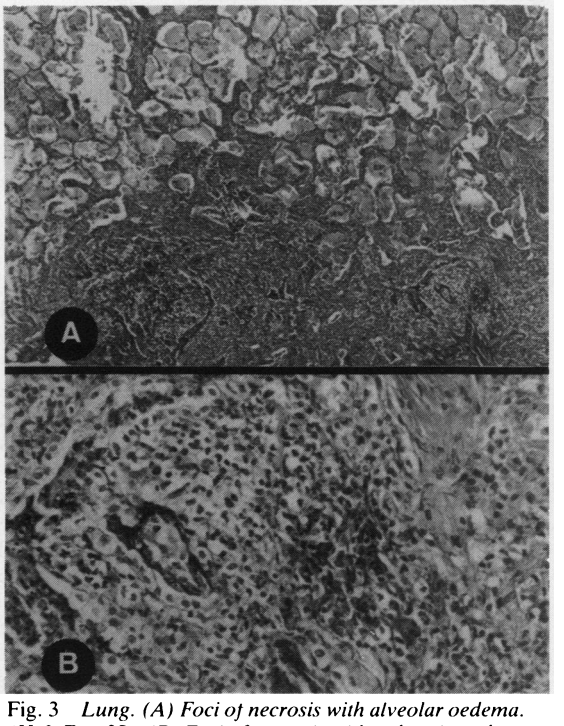

Fig. 3 *Lung. (A) Foci of necrosis with alveolar oedema. (H & E, ×35). (B) Foci of necrosis with pyknotic and coalescent nuclei surrounded by lymphomononuclear infiltrate. (H & E, ×35).*

In May 1982 the patient felt better. The subcutaneous nodules had almost disappeared and she had no dyspnoea, but the facial destruction was worsening. She also had intense morning bronchorrhoea. The prednisolone dose was reduced gradually.

In October 1982 the chest *x* ray showed some collapse of both inferior lobes, with alveolar infiltrate and dilatation of the airways. Pulmonary function tests showed less restriction and a slight change in the elasticity since 1981. The nose destruction was progressive.

In December 1982/January 1983 the patient felt better, but the facial destruction continued to progress. Radiotherapy was therefore given in a dose of 200 rads five times a week. A total of 4000 rads was administered. Two months after finishing the radiotherapy (March 1983) the patient developed a severe facial herpes infection with keratitis. She responded well to arabinoside A. At this stage cyclophosphamide was stopped.

Cyclophosphamide was restarted in June 1983. The ESR was 80 mm/1st h. The patient had dyspnoea upon physical effort, occasional fever, and intense morning bronchorrhoea, but great improvement was noticed after postural drainage. At this stage the facial destruction was not progressing.

In December 1983 cyclophosphamide was stopped. The patient had an ESR of 40 mm/1st h. Nine months after withdrawal of cyclophosphamide the patient was feeling better and gaining weight. She had continued to experience bronchorrhoea in the morning but was relieved by postural drainage. A chest *x* ray was similar to that taken in 1982, and the patient refused bronchography. The facial lesions had stabilised.

CASE 2

A 24 year old women, born after normal pregnancy and delivery, developed a non-painful nodule on the posterior aspect of the right thigh (3×3 cm) at the age of 16. This was removed for cosmetic reasons. The biopsy showed a granulomatous reaction, and no therapy was given. Subsequently she has married and had two normal pregnancies.

In June 1984, while we were reviewing her sister, we discovered that she had had thick, crusty nasal secretions, especially in the morning, for at least the past eight years. Physical examination was normal, apart from a perforation of the nasal septum. A biopsy was performed, and at the same time we reviewed the skin nodule biopsy done in 1976. The skin biopsy specimen showed granulomatous vasculitis, with fibrinoid necrosis, giant cells, and perian-

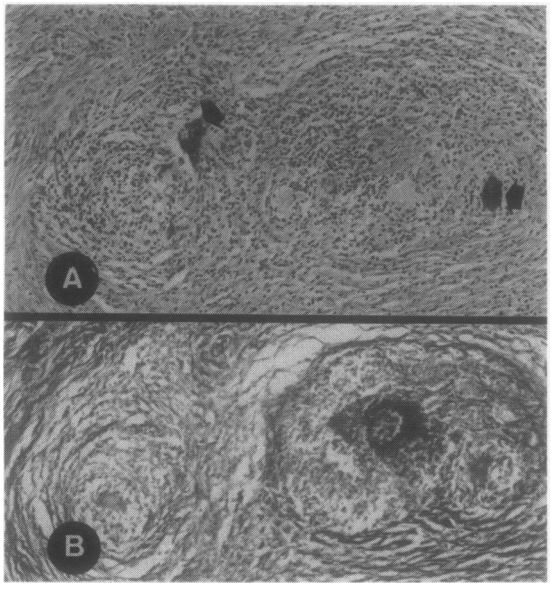

Fig. 4 *Skin biopsy specimen: (A) Necrotising granulomatous vasculitis with giant cells (arrows). (Haematoxylin and eosin, ×170). (B) Vessel wall destruction with fragmentation of the elastic lamina. (Verhoff's elastic stain, ×170).*

exial and perivascular lymphocyte infiltration (Fig. 4). The nasal mucosa biopsy specimen showed ulceration, necrosis, intense lymphocytic and histiocytic infiltration with occasional giant cells, and lymphocytic vasculitis; near the necrotic foci there was infiltration with neutrophils and eosinophils. The chest *x* ray was normal. Sinus *x* rays showed opacification of the maxillary and frontal sinuses. The ESR was 16 mm/1st h, and the remaining laboratory investigations were normal. The patient refused treatment.

Both sisters have always lived in an urban area and worked in a family owned supermarket. Their parents are alive and healthy, as is a third sister. Superoxide production, measured by cytochrome *c* reduction test, was normal in both patients.

Discussion

We believe that these two sisters have clinical and pathological changes compatible with or even typical of pathergic (Wegener's) granulomatosis.[8] Nevertheless, some peculiarities need to be considered.

Firstly, the age of onset: symptoms started at 8 and 15 years. The mean age of Wegener's and pathergic Wegener's disease is older, but classical Wegener's disease has been reported to begin at 8 years of age,[9] and pathergic granulomatosis at 12 years of age.[4]

Secondly, because of the familial clustering infectious or familial disease must be excluded. Bacteria, fungus, and parasites were searched for repeatedly in tissues and secretions. The only micro-organism found was *Staphylococcus aureus* in the first patient. This frequently superinfects these patients.[5] In the second patient nothing was found on culture. Although some patients with chronic granulomatous disease may survive in the first year of life, the clinical picture, the response to cytostatics, and the superoxide production ruled out this diagnosis.

The pathological findings in these patients are most consistent with Wegener's granulomatosis. With the first biopsy in both patients the diagnosis was missed. These were reported as 'granulomatous reactions', although a later review of the slides showed the classical appearances of pathergic (Wegener's) granulomatosis.

Tsokos *et al* grouped together the destructive lesions of the upper respiratory tract under the designation 'midline granuloma syndrome'.[10] This term includes infectious diseases, Wegener's disease, midline malignant reticulosis, lymphoma, carcinoma, and idiopathic midline destructive disease (IMDD).

We have not found any atypical lymphocytes in the vessels walls nor in the tissues, so that midline malignant granuloma is excluded.[11 12] The presence of multiple granulomas and the systemic involvement make a diagnosis of IMDD highly improbable. Such extensive necrosis, the lack of sarcoid-like granulomata, and the upper airways disease make necrotising sarcoid granulomatosis unlikely.[13]

It is generally considered that both generalised and localised Wegener's disease respond to therapy with cyclophosphamide.[14] Although there have been some therapeutic failures reported, these are generally thought to be due to the lesions being irreversible.[14] In the first and only case that has received therapy up to now the skin lesions responded very quickly, but the pulmonary lesions continued to progress. Seven months after the introduction of therapy the lung biopsy showed lesions in different stages, and the chest *x* ray was no better. Pulmonary function tests improved 10 months after starting therapy. In our case we believe that the bronchorrhoea was due to bronchiectasis.

The indications for radiotherapy in these patients are controversial. It has been reported that IMDD is the only one that responds to this form of therapy,[10] although there are exceptions to this.[6] Initially, in case 1 we considered changing the cytostatic drug

but then decided that the patient was responding well to cyclophosphamide. Two months after radiotherapy the facial lesions had improved. Although we cannot rule out the possibility that cyclophosphamide contributed to this improvement, the timing suggests that radiotherapy was responsible.

Case 2 has not yet been treated. We had discussed this with her. She is feeling well and does not wish to be treated at this stage.

In conclusion, we believe that these are the first cases of pathergic (Wegener's) granulomatosis described in one family, both with an early presentation. In the patient treated (case 1) the response to cyclophosphamide was slow and she had significant side effects. The fact that the second case was found by chance and was almost asymptomatic suggests that it may be important to look for it amongst the relatives of other patients with Wegener's disease. Finally, it may be that some patients with pathergic (Wegener's) granulomatosis who did not respond to cyclophosphamide may respond to radiation therapy.

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